REMARKS

In the final Office Action dated February 1, 2002, claims 666, 680, 681, 683, 685, 687-702, 704, 709-714, 716, 717, and 725 were allowed, and claims 23, 27-35, 38-40, 42-43, 52-53, 65, 69, 73, 81, 84, 95, 96, 104-110, 112-123, 127-135, 622, 624-650, 652-654, 656, 661, 667, 679-684, 703, 718-719, 724, 729-746, 757-759, 765, and 862-867 were rejected.

Applicants respectfully submit that no new matter has been added by way of the above amendments.

Applicants have amended the specification to correct minor typographical errors.

Applicant has provided the Examiner with an English translation of the Japanese Patent Applications No. 05194225 via fax on March 13, 2002.

I. List of All Pending Claims

For the convenience of the Examiner, a copy of pending claims, as they now stand in front of the Patent Office, is provided below:

23. (Amended thrice) A solid pharmaceutical composition in a dosage form that is not enteric-coated, comprising: active ingredients consisting essentially of:

(a) a non-enteric coated proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof, in an amount of approximately 5 mg to approximately 300 mg; and

(b) at least one buffering agent in an amount of approximately 0.1 mEq to approximately 2.5 mEq per mg of proton pump inhibitor provided that the buffering agent is in an amount sufficient to elevate gastric acid pH of the subject's stomach to prevent or inhibit

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gastric acid degradation of the non-enteric coated proton pump inhibitor and achieve sufficient bioavailability of the proton pump inhibitor in the subject to elicit a therapeutic effect; wherein the dosage form is selected from the group consisting of suspension tablet, chewable tablet, effervescent powder, and effervescent tablet.

27. (Amended) The composition as recited in Claim 23, wherein the proton pump inhibitor is omeprazole.

28. (Amended) The composition as recited in Claim 23, wherein the proton pump inhibitor is lansoprazole.

29. (Amended) The composition as recited in Claim 23, wherein the proton pump inhibitor is rabeprazole.

30. (Amended) The composition as recited in Claim 23, wherein the proton pump inhibitor is esomeprazole.

31. (Amended) The composition as recited in Claim 23, wherein the proton pump inhibitor is pantoprazole.

32. (Amended) The composition as recited in Claim 23, wherein the proton pump inhibitor is pariprazole.

33. (Amended) The composition as recited in Claim 23, wherein the proton pump inhibitor is leminoprazole.

34. (Amended) The composition as recited in Claim 23, further comprising at least one flavoring agent.

35. (Amended) The composition as recited in Claim 23, further comprising an anti-foaming agent.

38. (Amended) The composition as recited in Claim 23, wherein the dosage form is a suspension tablet.

39. (Amended) The composition as recited in Claim 23, wherein the dosage form is a chewable tablet.

40. (Amended) The composition as recited in Claim 39, further comprising aspartame.

42. (Amended) The composition as recited in Claim 23, wherein the dosage form is an effervescent powder.

43. (Amended) The composition as recited in Claim 23, wherein the dosage form is an effervescent tablet.

52. (Amended) The composition as recited in Claim 23, wherein the buffering agent is at least about 1680 mg sodium bicarbonate.

53. (Amended) The composition as recited in Claim 23, wherein the buffering agent is about 1000 mg to about 1680 mg sodium bicarbonate.

65. (Amended) A method of producing a liquid pharmaceutical composition, comprising: combining the composition recited in Claim 38 with an aqueous medium.

69. (Amended) A method of producing a liquid pharmaceutical composition, comprising: combining the composition recited in Claim 39 with an aqueous medium.

73. (Amended) A method of producing a liquid pharmaceutical composition, comprising: combining the composition recited in Claim 40 with an aqueous medium.

81. (Amended) A method of producing a liquid pharmaceutical composition, comprising: combining the composition recited in Claim 42 with an aqueous medium.

84. (Amended) A method of producing a liquid pharmaceutical composition, comprising: combining the composition recited in Claim 43 with an aqueous medium.

95. (Amended thrice) A method for treating an acid-caused gastrointestinal disorder in a subject in need thereof, comprising: administering to the subject the dosage form of claim 23 via a route selected from the group consisting of oral, nasogastric, and gastric tube.

96. (Amended) The method as recited in Claim 95, wherein the disorder is selected from the group consisting of duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease, erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, and acid dyspepsia.

104. (Amended) The method as recited in Claim 95, wherein the proton pump inhibitor is omeprazole.

105. (Amended) The method as recited in Claim 95, wherein the proton pump inhibitor is lansoprazole.

106. (Amended) The method as recited in Claim 95, wherein the proton pump inhibitor is rabeprazole.

107. (Amended) The method as recited in Claim 95, wherein the proton pump inhibitor is esomeprazole.

108. (Amended) The method as recited in Claim 95, wherein the proton pump inhibitor is pantoprazole.

109. (Amended) The method as recited in Claim 95, wherein the proton pump inhibitor is pariprazole.

110. (Amended) The method as recited in Claim 95, wherein the proton pump inhibitor is leminoprazole.

112. (Amended) The method as recited in Claim 95, wherein the composition further comprises a flavoring agent.

113. (Amended) The method as recited in Claim 95, wherein the composition further comprises an anti-foaming agent.

114. The method as recited in Claim 95, wherein the dosage form is a tablet.

115. The method as recited in Claim 95, wherein the dosage form is a powder.

116. The method as recited in Claim 95, wherein the dosage form is a suspension tablet.

117. The method as recited in Claim 95, wherein the dosage form is a chewable tablet.

118. The method as recited in Claim 117, wherein the dosage form further comprises aspartame.

119. The method as recited in Claim 95, wherein the dosage form is a capsule.

120. The method as recited in Claim 95, wherein the dosage form is an effervescent powder.

121. The method as recited in Claim 95, wherein the dosage form is an effervescent tablet.

122. (Amended) The method as recited in Claim 95, wherein the composition is a plurality of pellets.

123. (Amended) The method as recited in Claim 95, wherein the composition is a plurality of granules.

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127. The method as recited in Claim 95, wherein the buffering agent comprises a bicarbonate salt of a Group IA metal.

128. The method as recited in Claim 95, wherein the buffering agent comprises at least one of magnesium hydroxide, magnesium lactate, magnesium gluconate, magnesium oxide, magnesium carbonate, magnesium silicate, magnesium lactate, and other magnesium salts.

129. (Amended) The method as recited in Claim 95, wherein the buffering agent comprises at least one of calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium bicarbonate, calcium gluconate, or other calcium salts.

130. The method as recited in Claim 95, wherein the buffering agent comprises about 250 mg to about 1680 mg sodium bicarbonate.

131. The method as recited in Claim 95, wherein the buffering agent comprises about 840 mg to about 1680 mg sodium bicarbonate.

132. (Amended) The method as recited in Claim 95, wherein the buffering agent is about 250 mg to about 1000 mg calcium carbonate.

133. (Amended) The method as recited in Claim 95, wherein the buffering agent is about 500 mg to about 1000 mg calcium carbonate.

134. The method as recited in Claim 95, wherein the buffering agent comprises a combination of sodium bicarbonate and calcium carbonate.

135. The method as recited in Claim 95, further comprising combining the dosage form with an aqueous medium.

622. (Amended) A method for treating an acid-caused gastrointestinal disorder in a subject in need thereof, comprising: administering to the subject a solid pharmaceutical

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composition in a dosage form that is not enteric-coated; wherein the composition comprises active ingredients consisting essentially of:

(a) ~~(c)~~ a therapeutically effective amount of a non-enteric coated proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof; and

(b) ~~(d)~~ a buffering agent selected from the group consisting of a bicarbonate salt of a group IA metal, a calcium salt, and a magnesium salt, wherein the buffering agent is in an amount sufficient to elevate gastric acid pH of the subject's stomach to prevent or inhibit gastric acid degradation of the non-enteric coated proton pump inhibitor and achieve sufficient bioavailability of the proton pump inhibitor in the subject to elicit a therapeutic effect.

624. (Amended) The method of Claim 622, wherein the calcium salt is selected from the group consisting of calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium bicarbonate, calcium gluconate, and other calcium salts.

625. (Amended) The method of Claim 622, wherein the sodium bicarbonate is in an amount from about 1000 mg to about 1680 mg.

626. (Amended) The method of Claim 622, wherein the sodium bicarbonate is in an amount of at least about 1680 mg.

627. (Amended) The method of Claim 622, wherein the calcium salt is calcium carbonate present in an amount from about 250 mg to about 1000 mg.

628. (Amended) The method of Claim 622, wherein the calcium salt is calcium carbonate present in an amount from about 500 mg to about 1000 mg.

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629. (Amended) The method of Claim 622, wherein the calcium salt is calcium carbonate present in an amount of at least about 1000 mg.

630. (Amended) The method of Claim 622, wherein the buffering agent is in an amount of at least 10 mEq.

631. (Amended) The method of Claim 622, wherein the buffering agent is in an amount from about 10 mEq to about 70 mEq.

632. (Amended) The method of Claim 622, wherein the buffering agent is in an amount from about 20 mEq to about 40 mEq.

633. (Amended) The method of Claim 622, wherein the proton pump inhibitor is in an amount from about 10 mg to about 100 mg.

634. (Amended) The method of Claim 622, wherein the proton pump inhibitor is omeprazole.

635. (Amended) The method of Claim 634, wherein the omeprazole is present in an amount of about 10 mg.

636. (Amended) The method of Claim 634, wherein the omeprazole is present in an amount of about 20 mg.

637. (Amended) The method of Claim 634, wherein the omeprazole is present in an amount of about 40 mg.

638. (Amended) The method of Claim 634, wherein the omeprazole is present in an amount of about 60 mg.

639. (Amended) The method of Claim 634, wherein the omeprazole is present in an amount of about 80 mg.

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640. (Amended) The method of Claim 634, wherein the omeprazole is present in an amount of about 100 mg.

641. (Amended) The method of Claim 622, wherein the proton pump inhibitor is lansoprazole.

642. (Amended) The method of Claim 641, wherein the lansoprazole is present in an amount of about 15 mg.

643. (Amended) The method of Claim 641, wherein the lansoprazole is present in an amount of about 30 mg.

644. (Amended) The method of Claim 641, wherein the lansoprazole is present in an amount of about 45 mg.

645. (Amended) The method of Claim 641, wherein the lansoprazole is present in an amount of about 60 mg.

646. (Amended) The method of Claim 641, wherein the lansoprazole is present in an amount of about 90 mg.

647. (Amended) The method of Claim 641, wherein the lansoprazole is present in an amount of about 100 mg.

648. (Amended) The method of Claim 622, wherein the proton pump inhibitor is micronized.

649. (Amended) The method of Claim 622, wherein the composition is in a dosage form selected from the group consisting of a tablet, powder, suspension tablet, chewable tablet, capsule, effervescent powder, effervescent tablet, pellets, and granules.

650. (Amended) The method of Claim 622, wherein the subject is a human.

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652. (Amended) The method of Claim 622, wherein the dosage form further comprises a flavoring agent.

653. (Amended) The method of Claim 652, wherein the flavoring agent comprises aspartame, chocolate, root beer, peppermint, spearmint, or watermelon, and combinations of any of the foregoing.

654. (Amended) The method of Claim 622, wherein the composition is provided as a separate component of a kit.

656. (Amended) The method of Claim 622, wherein the disorder is selected from the group consisting of duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease, erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, and acid dyspepsia.

661. (Amended) The method of Claim 622, wherein the dosage form is administered once or twice a day.

666. **(Allowed)** A solid pharmaceutical composition in a dosage form that is not enteric-coated, comprising: active ingredients consisting essentially of:

(a) a therapeutically effective amount of a non-enteric coated proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof; and

(b) a buffering agent selected from the group consisting of sodium bicarbonate, and calcium carbonate, in an amount more than about 40 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

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667. (Amended) The composition as recited in Claim 666, wherein the amount of the buffering agent is sufficient to prevent or inhibit *in vivo* gastric acid degradation of the proton pump inhibitor upon the administration of the dosage form to a subject so as to achieve bioavailability of the proton pump inhibitor in the subject.

679. (Amended) The composition as recited in Claim 666, wherein the buffering agent is sodium bicarbonate.

680. **(Allowed)** The composition as recited in Claim 666, wherein the sodium bicarbonate is in an amount from about 400 mg to about 4000 mg.

681. **(Allowed)** The composition as recited in Claim 666, wherein the sodium bicarbonate is in an amount of at least about 800 mg.

682. (Amended twice) The composition as recited in Claim 666, wherein the buffering agent is calcium carbonate.

683. **(Allowed)** The composition as recited in Claim 666, wherein the calcium carbonate is in an amount from about 400 mg to about 4000 mg.

684. The composition as recited in Claim 682, wherein the calcium carbonate is in an amount from about 500 mg to about 1000 mg.

685. **(Allowed)** The composition as recited in Claim 682, wherein the calcium carbonate is in an amount of at least about 800 mg.

687. **(Allowed)** The composition as recited in Claim 666, wherein the proton pump inhibitor is in an amount from about 10 mg to about 100 mg.

688. **(Allowed)** The composition as recited in Claim 666, wherein the proton pump inhibitor is omeprazole.

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689. **(Allowed)** The composition as recited in Claim 688, wherein the omeprazole is present in an amount of about 10 mg.

690. **(Allowed)** The composition as recited in Claim 688, wherein the omeprazole is present in an amount of about 20 mg.

691. **(Allowed)** The composition as recited in Claim 688, wherein the omeprazole is present in an amount of about 40 mg.

692. **(Allowed)** The composition as recited in Claim 688, wherein the omeprazole is present in an amount of about 60 mg.

693. **(Allowed)** The composition as recited in Claim 688, wherein the omeprazole is present in an amount of about 80 mg.

694. **(Allowed)** The composition as recited in Claim 688, wherein the omeprazole is present in an amount of about 100 mg.

695. **(Allowed)** The composition as recited in Claim 666, wherein the proton pump inhibitor is lansoprazole.

696. **(Allowed)** The composition as recited in Claim 695, wherein the lansoprazole is present in an amount of about 15 mg.

697. **(Allowed)** The composition as recited in Claim 695, wherein the lansoprazole is present in an amount of about 30 mg.

698. **(Allowed)** The composition as recited in Claim 695, wherein the lansoprazole is present in an amount of about 45 mg.

699. **(Allowed)** The composition as recited in Claim 695, wherein the lansoprazole is present in an amount of about 60 mg.

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700. **(Allowed)** The composition as recited in Claim 695, wherein the lansoprazole is present in an amount of about 90 mg.

701. **(Allowed)** The composition as recited in Claim 695, wherein the lansoprazole is present in an amount of about 100 mg.

702. **(Allowed)** The composition as recited in Claim 666, wherein the proton pump inhibitor is micronized.

703. The composition as recited in Claim 666, wherein the composition is in a dosage form selected from the group consisting of a tablet, powder, suspension tablet, chewable tablet, capsule, effervescent powder, effervescent tablet, pellets, and granules.

704. **(Allowed)** The composition as recited in Claim 666, further comprising a flavoring agent comprising aspartame, chocolate, root beer, peppermint, spearmint, or watermelon, and combinations of any of the foregoing.

709. **(Allowed)** The composition as recited in Claim 666, wherein the amount of the buffering agent is more than about 50 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

710. **(Allowed)** The composition as recited in Claim 666, wherein the amount of the buffering agent is more than about 60 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

711. **(Allowed)** The composition as recited in Claim 666, wherein the amount of the buffering agent is more than about 70 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

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712. **(Allowed)** The composition as recited in Claim 666, wherein the amount of the buffering agent is more than about 80 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

713. **(Allowed)** The composition as recited in Claim 666, wherein the amount of the buffering agent is more than about 90 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

714. **(Allowed)** The composition as recited in Claim 666, wherein the amount of the buffering agent is more than about 100 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

716. **(Allowed)** The composition as recited in Claim 666, wherein the composition is provided as a separate component of a kit.

717. **(Allowed)** A method of producing a liquid pharmaceutical composition comprising: combining the dosage form of Claim 666 with an aqueous medium.

718. (Amended twice) A method for treating an acid-caused gastrointestinal disorder in a subject in need thereof, comprising: administering to the subject the dosage form as recited in Claim ~~666~~ via a route selected from the group consisting of oral, nasogastric, and gastric tube.

719. (Amended) The method as recited in Claim 718, wherein the disorder is selected from the group consisting of duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease, erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, and acid dyspepsia.

724. The method as recited in Claim 718, wherein the composition is administered once or twice a day.

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725. **(Allowed)** A method for administering a liquid pharmaceutical composition to a subject, comprising: combining the pharmaceutical composition as recited in Claim 666 with an aqueous medium to form a suspension, and orally administering the suspension to the subject in a single dose without administering an additional buffering agent.

729. The composition as recited in Claim 23, wherein the proton pump inhibitor is in an amount from about 10 mg to about 100 mg.

730. The composition as recited in Claim 729, wherein the proton pump inhibitor is omeprazole.

731. The composition as recited in Claim 729, wherein the omeprazole is present in an amount of about 10 mg.

732. The composition as recited in Claim 729, wherein the omeprazole is present in an amount of about 20 mg.

733. The composition as recited in Claim 729, wherein the omeprazole is present in an amount of about 40 mg.

734. The composition as recited in Claim 729, wherein the omeprazole is present in an amount of about 60 mg.

735. The composition as recited in Claim 729, wherein the omeprazole is present in an amount of about 80 mg.

736. The composition as recited in Claim 729, wherein the omeprazole is present in an amount of about 100 mg.

737. The composition as recited in Claim 729, wherein the proton pump inhibitor is lansoprazole.

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738. The composition as recited in Claim 737, wherein the lansoprazole is present in an amount of about 15 mg.

739. The composition as recited in Claim 737, wherein the lansoprazole is present in an amount of about 30 mg.

740. The composition as recited in Claim 737, wherein the lansoprazole is present in an amount of about 45 mg.

741. The composition as recited in Claim 737, wherein the lansoprazole is present in an amount of about 60 mg.

742. The composition as recited in Claim 737, wherein the lansoprazole is present in an amount of about 90 mg.

743. The composition as recited in Claim 737, wherein the lansoprazole is present in an amount of about 100 mg.

744. The composition as recited in Claim 23, wherein the proton pump inhibitor is micronized.

745. The composition as recited in Claim 34, wherein the flavoring agent comprises aspartame, chocolate, root beer, peppermint, spearmint, or watermelon, and combinations of any of the foregoing.

746. The composition as recited in Claim 23, wherein the composition is provided as a separate component of a kit.

757. The method as recited in Claim 95, wherein the proton pump inhibitor is in an amount from about 10 mg to about 100 mg.

758. The method as recited in Claim 95, wherein the proton pump inhibitor is micronized.

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759. The method as recited in Claim 112, wherein the flavoring agent comprises aspartame, chocolate, root beer, peppermint, spearmint, or watermelon, and combinations of any of the foregoing.

765. The method as recited in Claim 95, wherein the composition is administered once or twice a day.

862. The composition of Claim 23, wherein the buffering agent comprises a bicarbonate salt of a Group IA metal.

863. The composition of Claim 23, wherein the buffering agent comprises at least one of magnesium hydroxide, magnesium lactate, magnesium gluconate, magnesium oxide, magnesium carbonate, or magnesium silicate.

864. The composition of Claim 23, wherein the buffering agent comprises at least one of calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, calcium gluconate, or other calcium salts.

865. The composition of Claim 23, further comprising a disintegrant, flow aid, lubricant, adjuvant, excipient, colorant, diluent, moistening agent, preservative, and pharmaceutically compatible carrier.

866. The method of claim 95, wherein the composition further comprises a disintegrant, flow aid, lubricant, adjuvant, excipient, colorant, diluent, moistening agent, preservative, and pharmaceutically compatible carrier.

867. The method of claim 622, wherein the composition further comprises a disintegrant, flow aid, lubricant, adjuvant, excipient, colorant, diluent, moistening agent, preservative, and pharmaceutically compatible carrier.

II. Rejections Under 35 U.S.C. § 112, First Paragraph

a. **Claims 23, 27-35, 38-40, 42-43, 52-53, 65, 69, 73, 81, 84, 95-96, 104-110, 112-123, 127-135, 680-684, 729-746, 757-759, 765, 862-865**

The Examiner rejected claims 23, 27-35, 38-40, 42-43, 52-53, 65, 69, 73, 81, 84, 95-96, 104-110, 112-123, 127-135, 680-684, 729-746, 757-759, 765, 862-865 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner stated that it is not clear how the weight ratio was derived for all PPI's and all kinds of "at least one buffering agent" and their combinations and permutation thereof. The Examiner further stated that the specification does not have any antecedent basis or support for the newly claimed language.

The Applicant respectfully disagrees and traverses this rejection. Under 35 U.S.C. § 112, first paragraph, it is only required that the specification describe the invention sufficiently for those of ordinary skill in the art to recognize that the applicant invented the subject matter he now claims. *In re Voss* 194 USPQ 267, 271 (CCPA 1977).

Although the Office Action states that the "specification does not have any antecedent basis or support for the newly claimed language," Applicant again emphasizes to the Examiner that each element of the claims is clearly disclosed in the specification as originally filed. The Examiner's attention is respectfully directed to the following disclosure in the Specification as originally filed, which provides antecedent basis and support for each of the claimed elements:

(i) Page 24, lines 19-23: "Such dosage forms...comprise a PPI and at least one buffering agent...."

(ii) Page 26, lines 19-27: "For the purposes of this application, the term 'proton pump inhibitor' (PPI) shall mean any substituted benzimidazole possessing pharmacological activity as an inhibitor or H^+, K^+-ATPase, including, but not limited to [the list of PPIs]."

(iii) Page 30, lines 15-21: "For the purposes of this application, 'buffering agent' shall mean any pharmaceutically appropriate weak base or strong base (and mixtures thereof) that when formulated or delivered with...the PPI, functions to substantially prevent or inhibit the acid degradation of the PPI by gastric acid sufficient to preserve the bioavailability of the PPI administered."

(iv) Page 28, lines 18-21: "The dosage range of omeprazole or other proton pump inhibitors such as substituted benzimidazoles and derivatives thereof can range from approximately <2 mg/day to approximately 300 mg/day."

(v) Page 31 states that the solution can be formulated with 5% to 60% sodium bicarbonate, which equates to about 5 mEq to about 70 mEq per 10 ml dose of omeprazole.

(vi) Page 32, lines 1-5: "approximately 1 mEq . . . sodium bicarbonate per 2 mg omeprazole with a range of approximately 0.2 mEq . . . to 5 mEq . . . per 2 mg omeprazole."

(vii) Page 33, lines 26-29: "The omeprazole or other PPIs and buffering agent can be formed into a tablet, capsule . . . ."

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(viii) Page 26, lines 28-30: "The inventive compositions comprise dry forms, solutions and/or suspensions of the proton pump inhibitors."

(ix) Page 35, lines 11-13: "[T]he suspension tablets comprise about 20 mg omeprazole and about 1-20 mEq of sodium bicarbonate."

(x) Page 26, lines 11-17: "While the present invention may be embodied in many different forms, several specific embodiments are discussed herein with the understanding that the present disclosure is to be considered only an exemplification of the principles of the invention, and it is not intended to limit the invention to the embodiments illustrated."

(xi) Pages 45-47: Solid dosage form Examples.

From this disclosure, one skilled in the relevant art would clearly appreciate that Applicant had derived weight ratio for all of the PPI's and the buffering agents of the present invention. Reconsideration and withdrawal of this rejection is respectfully requested.

b. **Claims 95, 96, 104-110, 112-123, 127-135, 622, 624-650, 652-654, 656, 661, 718-719, 724, 757-759, 765, and 866-867**

The Examiner rejected claims 95, 96, 104-110, 112-123, 127-135, 622, 624-650, 652-654, 656, 661, 718-719, 724, 757-759, 765, and 866-867 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for omeprazole for hypersecretion only does not reasonably provide enablement for all PPI's for all acid related diseases. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate with these claims.

The Applicant respectfully disagrees and traverses this rejection. Under 35 U.S.C. § 112, first paragraph, it is only required that the specification describe the invention sufficiently for those of ordinary skill in the art to recognize that the applicant invented the subject matter he now claims. *In re Voss* 194 USPQ 267, 271 (CCPA 1977).

In particular the Examiner stated that the following three reasons for the rejection apply:

(i) Examiner's Reason #1: Acid Related GI Disorder

The Examiner stated: That an "'[a]cid related disorder' read[s] on too little acid which is beyond enablement."

Independent claims 95, 622, and 718 have been amended to better define the invention. Additionally, one skilled in the art reading the specification would recognize that the present invention claims, among other things, proton pump inhibitors, which for the purposes of this application means any substituted benzimidazole possessing pharmacological activity as an inhibitor or H^+, K^+-ATPase and is acid labile. Several illustrative examples are provided. (See page 26, lines 19-27).

One skilled in the art would recognize that drugs of this class suppress gastric acid secretion by the specific inhibition of the H^+,K^+-ATPase enzyme system (proton pump) at the secretory surface of the gastric parietal cell. (See page 1, lines 21-24)

One skilled in the relevant art would also recognize that typically, omeprazole, lansoprazole and other proton pump inhibitors are formulated in an enteric-coated solid dosage form (as either a delayed-release capsule or tablet) or as an intravenous solution (or as a product for reconstitution), and are prescribed for short-term treatment of active duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive systematic GERD, and pathological hypersecretory conditions such as Zollinger Ellison

syndrome. These conditions are caused by an imbalance between acid and pepsin production, called aggressive factors, and mucous, bicarbonate, and prostaglandin production, called defensive factors. These above-listed conditions commonly arise in healthy or critically ill patients, and may be accompanied by significant upper gastrointestinal bleeding. (See page 1, line 24, through page 2, line10)

Thus, Applicant contends that the specification describes the invention sufficiently for one of ordinary skill in the art to recognize that the applicant invented the subject matter he now claims, which, among other things, is the suppression of gastric acid secretion by specific inhibition of the H^+,K^+-ATPase enzyme system. Therefore, the scope of enablement is commensurate with the scope of protection sought by the claims. Reconsideration and withdrawal of this rejection is respectfully requested.

(ii) Examiner's Reason #2: Nasogastric Tube Administration

The Examiner states that: "It is not understood how a solid composition can be administered through a nasogastric or gastric tube. It appears that the tube would be totally congested." Applicant traverses this point as follows.

First, as is known in the art, any solid to be given by these routes will first be crushed and/or mixed or delivered with a liquid to avoid clogging. The compositions of the present invention are to be administered in accordance with good medical practice, taking into account the clinical condition of the individual patient, the site and method of administration, scheduling of administration, and other factors known to medical practitioners. (See page 28, lines 6).

Second, the Specification provides that the formulations of the present invention when administered via a nasogastric tube or other indwelling tube placed in the GI tract are in the form

of a solution or suspension. (See page 28, line 30, through page 29, line 2). On page 34, lines 16-26, of the Specification, it is provided that:

> "[T]he formulations of the present invention can also be manufactured in concentrated forms, such as tablets, suspension tablets and effervescent tablets or powders, such that upon reaction with water or other diluent, the aqueous form of the present invention is produced for oral, enteral or parenteral administration. The present pharmaceutical tablets or other solid dosage forms disintegrate rapidly in aqueous media and form an aqueous solution of the PPI and buffering agent with minimal shaking or agitation.

Third, it is well understood that an inventor need not explain every detail since he is speaking to those skilled in the art. What is conventional knowledge will be read into the disclosure. *In re Howarth*, 210 USPQ 689, 692 (CCPA 1981). Accordingly, an applicant's duty to tell all that is necessary to make or use varies greatly depending upon the art to which the invention pertains. It is well settled that the disclosure of an application embraces not only what is expressly set forth in words or drawings, but what would be understood by persons skilled in the art. As was stated in *Webster Loom Co. v. Higgins et al.*, 105 U.S. 580, 586, the applicant "may begin at the point where his invention begins, and describe what he has made that is new and what it replaces of the old. That which is common and well known is as if it were written out in the patent and delineated in the drawings."

Therefore, the specification describes the invention sufficiently for those of ordinary skill in the art to recognize that the applicant invented the subject matter he now claims. Reconsideration and withdrawal of this rejection is requested.

(iii) Examiner's Reason #3: Premixed v. Step-wise Administration

The Examiner stated that: "For claim 622 and all dependent claims thereof, it is noted that the claimed language is not clear whether the composition is premixed (prepared as a single dose) for administration or the administration is step-wise (sequential) because in part (b) it is

not able to monitor because it would be too difficult or too late to evaluate pH of a patient for proper treatment."

The Applicant respectfully disagrees and traverses this rejection. First, as the claims now stands in front of the Patent Office, claim 622 and its dependent claims, claims a solid pharmaceutical composition. Inherent in this is that the composition must be made up of certain elements. In this case, the composition comprises active ingredients. These active ingredients consist essentially of two elements (a) and (b). Element (a) is a non-enteric coated proton pump inhibitor. Element (b) is a buffering agent. **This solid composition is then administered to the subject; no mixing or stepwise administration is required.**

Second, Applicant's use of functional language in (b) is proper to define the amount of buffering agent. The Examiner has objected to the use of such functional language. However, MPEP § 2173.05 (g) specifically permits functional limitations. In the Fuetterer case, the CCPA held that a 35 U.S.C. § 112 rejection of a claimed term does not depend upon whether it is functional, but whether the specification supports the use of this claimed term. In this regard, the CCPA stated:

> "Appellant has described his invention as comprehending the use therein of any inorganic salt capable of performing a specific function in a specific combination and he has disclosed specifically four such salts which are capable of performing this function.... The invention description clearly indicates that any inorganic salt which has such properties is usable in this combination."

In re Fuetterer 138 USPQ 217, 223 (CCPA 1963). See also MPEP § 2173.05 (g), Functional Limitations.

In the present claimed invention, the Specification clearly supports the use of the claimed terms. For example, on page 30, lines 15-24, the Specification provides that:

> "For purposes of this application, [the] "buffering agent"..., formulated or delivered with ...the PPI, functions to substantially prevent or inhibit the acid degradation of the PPI by gastric acid sufficient to preserve the bioavailability of the PPI administered. The buffering agent is administered in an amount sufficient to substantially achieve the above functionality."
>
> (emphasis added).

Similar to the Fuetterer case, claim 622 (and 667) defines the amount of buffer by what it does rather than what it is. Furthermore, one skilled in the art can determine from the written description and its examples the amount of buffer necessary to perform the disclosed functionality. Such determinations would not be beyond the skill of the art nor would it involve undue experimentation to ascertain. Furthermore, several studies performed by the Applicant demonstrating the functionality of the buffering agent are provided in the Specification, for example, see:

(i) Example V, Page 51,

(ii) Example VII, Page 66, and

(iii) Example VIII, Page 68.

Several prophetic examples are also provided in the Specification, for example, see:

(i) Example VI, Page 51,

(ii) Example XI, Page 84, and

(iii) Example XII, Page 88.

Furthermore, on page 35, lines 11-13, of the Specification, one finds one of the many examples disclosed describing the amount of buffer that can be used in the present claimed invention:

> "...the suspension tablets comprise about 20 mg omeprazole and about 1-20 mEq of sodium bicarbonate."

Thus, the specification clearly supports the use of the claimed terms.

In *In re Swinehart*, 439 F.2d 210, 169 USPQ 226, 228-29 (C.C.P.A. 1971), the court stated that there "was nothing intrinsically wrong with the use of such a technique [that is, functional language] in drafting patent claims." This court had even recognized "the practical necessity for the use of functional language."

There is ample precedent to establish that functional limitations are appropriate in composition claims and should be afforded patentable weight by the Examiner. (See, for example, MPEP § 2173.05 (g), and *In re Ludtke*, 441 F.2d 660, 169 USPQ 653, 566 (C.C.P.A. 1971)).

Therefore, Applicant contends that the Specification describes the invention sufficiently for those of ordinary skill in the art to recognize that the applicant invented the subject matter he now claims. Reconsideration and withdrawal of this rejection is requested.

III. Rejections Under 35 U.S.C. § 112, Second Paragraph

a. Claim 667

The Examiner rejected claim 667 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated that the composition cannot be prepared or shelved.

The Applicant respectfully disagrees and traverses this rejection. In rejecting a claim under 35 U.S.C. § 112, second paragraph, the Examiner must establish that one of ordinary skill in the pertinent art, when reading the claim in light of the supporting specification, would not have been able to ascertain with a reasonable degree of precision and particularity the specific area set out and circumscribed by the claim. *Ex parte Wu*, 10 USPQ 2d 2031m 2033 (B.P.A.I. 1989). As explained above, using functional language is permitted. Thus, the rejection of this claim based upon the use of functional language to define the amount of buffering agent in the composition is improper and should be withdrawn. Reconsideration and withdrawal of the this rejection is respectfully requested.

b. Claims 679, 683, and 684

The Examiner rejected claims 679, 683, and 684 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated that these claims are improper because the term "comprising."

It is respectfully brought to the attention of the Examiner that claim 684 does not contain the term "comprising." Therefore, the rejection of claim 684 is improper and should be withdrawn. Withdrawal of this rejection is respectfully requested.

Claims 679 and 683 have been amended to better define the invention. Withdrawal of this rejection is respectfully requested.

c. Claim 703

The Examiner rejected claim 703 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. The Examiner stated that the claim is confusing regarding the term "suspension tablet."

In rejecting a claim under 35 U.S.C. § 112, second paragraph, the Examiner must establish that one of ordinary skill in the pertinent art, when reading the claim in light of the supporting specification, would not have been able to ascertain with a reasonable degree of precision and particularity the specific area set out and circumscribed by the claim. *Ex parte Wu*, 10 USPQ 2d 2031m 2033 (B.P.A.I. 1989).

The Examiner's attention is respectfully directed to page 35, lines 5-11, of the Specification as originally filed:

> "The term 'suspension tablet' as used herein refers to compressed tablets which rapidly disintegrate after they are placed in water, and are readily dispersible to form a suspension containing a precise dosage of the PPI."

Applicants maintain that the term "'suspension tablet" when read in light of the supporting specification clearly defines the metes and bounds of the invention and clearly sets forth the subject matter of the invention. Withdrawal of this rejection is respectfully requested.

IV. Rejections Under 35 U.S.C. § 103(a)

The Examiner rejected claim 23 and all its dependent claims under 35 U.S.C. § 103(a) as being unpatentable over art of record for reasons of record. The Examiner stated that in patent law, that where patentability is based on a change in pH in a composition, such change must be "critical." The Examiner further states that it must lead to a new and unexpected result.

The Applicant respectfully disagrees and traverses this rejection. Additionally, the Applicant incorporates the arguments presented in the previous responses to this rejection and would like to reemphasize the following:

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a. Patentability of Claim 23 is Not Based on pH Change in the Composition

It is respectfully brought to the Examiner's attention that the patentability of claim 23 is not based on a change in pH in a composition. As the claims now stands in front of the Patent Office, claim 23 claims a solid pharmaceutical composition in a dosage form that is not enteric-coated, comprising an active ingredient consisting essentially of a non-enteric coated proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof, in an amount of approximately 5 mg to approximately 300 mg; and at least one buffering agent in an amount of approximately 0.1 mEq to approximately 2.5 mEq per mg of proton pump inhibitor, provided that the amount of agent is sufficient to protect the PPI as claimed. Also, the solid composition is in a suspension tablet, chewable tablet, effervescent powder, or effervescent tablet dosage form.

b. Establishing Prima Facie Case of Obviousness Lies with the Examiner

It is well established that the burden of establishing a *prima facie* case of obviousness lies with the Examiner. In determining obviousness, one must focus on the invention as a whole. *Symbol Technologies Inc. v. Opticon Inc.*, 19 USPQ 2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is: "Whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success.... Both the suggestion and the expectation of success must be found in the prior art, not the applicant's disclosure." *In re Dow Chemical*, 5 USPQ 2d 1531 (Fed. Cir. 1988). When all the prior art is considered together, a person having ordinary skill in the art must have a sufficient basis for the necessary predictability of success to sustain a rejection under 35 U.S.C § 103. See Ex parte Novitski 26 USPQ2d 1389 (Bd.Pat.App. & Int. 1993) Citing In re Clinton, 188 USPQ 365 (CCPA 1976).

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The cited references do not teach or suggest to one of ordinary skill in the art the present claimed invention, particularly the presently claimed dosage forms. There is no teaching or suggestion that the compositions in the cited references could be, for example, chewed or in any way ingested without a protective enteric coating to prevent acid degradation of the PPI in the gastrointestinal tract. The only teaching or suggestion for the buffering agent in the cited references is to protect the PPI from degradation caused by the enteric coating layer. Thus, these references do not provide one of ordinary skill in the art that the present claimed invention would have had a reasonable likelihood of success.

Again, both the suggestion and the expectation of success must be found in the prior art, not the applicant's disclosure. From the cited references, a person having ordinary skill in the art would not have a sufficient basis for the necessary predictability of success to sustain a rejection under 35 U.S.C § 103.

c. Ooishi '224 and '225 Teach Away from the Dosage Forms of Claim 23

Ooishi '224 and '225 do not render obvious Applicant's claims to solid compositions in non-enteric coated dosage forms, and particularly not the suspension tablet, chewable tablet, effervescent powder, or effervescent tablet dosage forms of claim 23. These references teach away from Applicant's claimed invention by emphasizing that suitable dosage forms must employ buffering agents **and** enteric coatings. There is thus a teaching away from the interaction in the stomach of a proton pump inhibitor and the low pH gastric secretions. Such teaching away rebuts obviousness. See In re Sponnoble, 405 F.2d 578, 587 (CCPA 1969); In re Caldwell, 319 F.2d 254, 256 (CCPA 1963).

d. Non-enteric Coating Dosage Forms Thought Unworkable by Skilled Artisans

Until the present invention, those skilled in the art thought that the administration of an acid labile proton pump inhibitor without an enteric coating to be unworkable. Applicant

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recognized the problems associated with the enteric coated dosage forms (e.g., lack of liquid forms, difficulty in swallowing by children, elderly and critically ill, slow onset of action, difficulty of manufacture, etc.) and solved them by the present invention. Consequently, Applicant's claims to dosage forms, and compositions employing non-enteric-coated proton pump inhibitors are not obvious.

e. No Reason, Suggestion, or Motivation to Make Combination of Present Invention

According to the Federal Circuit in In re Oetiker, 977 F.2d 1443, 1447 (Fed. Cir. 1992, "[t]here must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination." Here, as shown above, the prior art tells the skilled artisan that proton pump inhibitors must be enteric-coated or mixed with other active drugs and, thus, there was no teaching or suggestion of the present claimed invention.

f. No Suggestion for Oral Administration of Uncoated Intermediate Cores

The present claims recite dosage forms free of enteric coatings and which are not shielded from interacting with gastric acid secretions, and are specifically designed for disintegration and dissolution in the stomach whereas the enteric forms disintegrate and dissolve in the duodenum. None of the cited references teach or suggest the oral administration of the uncoated intermediate cores, nor do the cores meet the limitations of the present claims, for example, the dosage forms of claim 23 are a suspension tablet, a chewable tablet, an effervescent powder, or an effervescent tablet. Consequently, there is no teaching that such intermediate cores interact with gastric secretions to form the composition as claimed by Applicant. Indeed, the prior art teaches that such cores must have enteric coatings.

g. Conclusion

There is no teaching or suggestion of the present claimed invention in the cited references, nor is there any expectation of success found in these references. The Office Action also does not point to any portion of the cited references having the restriction of the dosage forms of claim 23 of a suspension tablet, a chewable tablet, an effervescent powder, or an effervescent tablet. Nor does the Office Action show any sound basis for believing the dosage forms of the present claimed invention and those of the cited references are the same. On the contrary, the primary cited references teach away from the presently claimed dosage forms. This 35 U.S.C. § 103 rejection is therefore improper and should be withdrawn.

Reconsideration and withdrawal of this rejection is respectfully submitted.

V. Conclusion

With entry of the above Amendment and in view of the foregoing remarks, it is respectfully submitted that claims 23, 27-35, 38-40, 42-43, 52-53, 65, 69, 73, 81, 84, 95, 96, 104-110, 112-123, 127-135, 622, 624-650, 652-654, 656, 661, 667, 679-684, 703, 718-719, 724, 729-746, 757-759, 765, and 862-867 are in condition for allowance.

Also submitted below, on a separate page titled "Version with Marking to Show Changes Made to the Claims," is a marked-up copy of prior pending claims and the specification. It is respectfully submitted in view of the foregoing Amendment and Remarks that all of the objections and rejections in the Office Action dated February 1, 2001 have been overcome and should be withdrawn. Applicant respectfully requests early and favorable notification to that effect. The Examiner is encouraged to contact the undersigned with any questions or to otherwise expedite prosecution.

Respectfully submitted,

THE CURATORS OF THE
UNIVERSITY OF MISSOURI

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By: _____
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Version with Markings to Show Changes Made to the Claims

23. (Amended thrice) A solid pharmaceutical composition in a dosage form that is not enteric-coated, comprising: active ingredients consisting essentially of:

(a) a non-enteric coated proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof, in an amount of approximately 5 mg to approximately 300 mg; and

(b) at least one buffering agent in an amount of approximately 0.1 mEq to approximately 2.5 mEq per mg of proton pump inhibitor provided that the buffering agent is in an amount sufficient to elevate gastric acid pH of the subject's stomach to prevent or inhibit gastric acid degradation of the non-enteric coated proton pump inhibitor and achieve sufficient bioavailability of the proton pump inhibitor in the subject to elicit a therapeutic effect;

wherein the dosage form is selected from the group consisting of suspension tablet, chewable tablet, effervescent powder, and effervescent tablet.

95. (Amended thrice) A method for treating an acid-caused [related] gastrointestinal disorder in a subject in need thereof, comprising: administering to the subject the dosage form of claim 23 via a route selected from the group consisting of oral, nasogastric, and gastric tube.

622. (Amended) A method for treating an acid-caused [related] gastrointestinal disorder in a subject in need thereof, comprising: administering to the subject a solid pharmaceutical composition in a dosage form that is not enteric-coated; wherein the composition comprises active ingredients consisting essentially of:

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(a) a therapeutically effective amount of a non-enteric coated proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof; and

(b) a buffering agent selected from the group consisting of a bicarbonate salt of a group IA metal, a calcium salt, and a magnesium salt, wherein the buffering agent is in an amount sufficient to elevate gastric acid pH of the subject's stomach to prevent or inhibit gastric acid degradation of the non-enteric coated proton pump inhibitor and achieve sufficient bioavailability of the proton pump inhibitor in the subject to elicit a therapeutic effect.

679. (Amended) The composition as recited in Claim 666, wherein the buffering agent is [comprises] sodium bicarbonate.

682. (Amended twice) The composition as recited in Claim 666, wherein the buffering agent is [comprises] calcium carbonate.

718. (Amended twice) A method for treating an acid-caused [related] gastrointestinal disorder in a subject in need thereof, comprising: administering to the subject the dosage form as recited in Claim 666 via a route selected from the group consisting of oral, nasogastric, and gastric tube.

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Version with Markings to Show Changes Made to the Specification

1. The paragraph beginning on page 2, line 23, has been amended as follows:

-- Patients with significant physiologic stress are at risk for stress-related gastric mucosal damage and subsequent upper gastrointestinal bleeding (Marrone and Silen, *Pathogenesis, Diagnosis and Treatment of Acute Gastric Mucosa Lesions,* CLIN GASTROENTEROL 13: 635-650 (1984)). Risk factors that have been clearly associated with the development of stress-related mucosal damage are mechanical ventilation, coagulopathy, extensive burns, head injury, and organ transplant (Zinner et al., *The Prevention of Gastrointestinal Tract Bleeding in Patients in an Intensive Care Unit,* SURG. GYNECOL. OBSTET., 153: 214-220 (1981); Larson et al., *Gastric Response to Severe Head Injury,* AM. J. SURG. 147: 97-105 (1984); Czaja et al., *Acute Gastroduodenal Disease After Thermal Injury: An Endoscopic Evaluation of Incidence and Natural History,* N ENGL. J. MED, 291: 925-929 (1974); Skillman et al., *Respiratory Failure, Hypotension, Sepsis and Jaundice: A Clinical Syndrome Associated with Lethal Hemorrhage From Acute Stress Ulceration,* AM. J. SURG., 117: 523-530 (1969); and Cook et al., *Risk Factors for Gastrointestinal Bleeding in Critically Ill Patients,* N. ENGL. J. MED., 330:377-381 (1994)). One or more of these factors are often found in critically ill, intensive care unit patients. A recent cohort study challenges other risk factors previously identified such as acid-base disorders, multiple trauma, significant hypertension, major surgery, multiple operative procedures, acute renal failure, sepsis, and coma (Cook et al., *Risk Factors for Gastrointestinal Bleeding in Critically Ill Patients,* N. ENGL. J. MED., 330:377-381 (1994)). Regardless of the risk type, stress-related mucosal damage results in significant morbidity and mortality. Clinically significant bleeding occurs in at least twenty percent of patients with one or more risk factors who are left untreated (Martin et al., *Continuous Intravenous* [*cimetidine*] <u>*Cimetidine*</u>

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Decreases Stress-related Upper Gastro-intestinal Hemorrhage Without Promoting Pneumonia, CRIT. CARE MED., 21: 19-[39] 30 (1993)). Of those who bleed, approximately ten percent require surgery (usually gastrectomy) with a reported mortality of thirty percent to fifty percent (Czaja et al., *Acute Gastroduodenal Disease After Thermal Injury: An Endoscopic Evaluation of Incidence and Natural History,* N ENGL. J. MED, 291: 925-929 (1974); Peura and Johnson, *Cimetidine for Prevention and Treatment of Gastroduodenal Mucosal Lesions in Patients in an Intensive Care Unit,* ANN INTERN MED., 103: 173-177 (1985)). Those who do not need surgery often require multiple transfusions and prolonged hospitalization. Prevention of stress-related upper gastrointestinal bleeding is an important clinical goal.--

2. The paragraph beginning on page 4, line 10, has been amended as follows:

--In addition to general supportive care, the use of drugs to prevent stress-related mucosal damage and related complications is considered by many to be the standard of care (AMA Drug Evaluations). However, general consensus is lacking about which drugs to use in this setting (Martin et al., *Continuous Intravenous Cimetidine Decreases Stress-related Upper Gastrointestinal Hemorrhage Without Promoting Pneumonia,* CRIT. CARE MED., 21: 19-[39] 30 (1993); Gafter et al., *Thrombocytopenia Associated With Hypersensitivity to Ranitidine: Possible Cross-reactivity with Cimetidine,* AM. J. GASTROENTEROL, [64] 84: 560-562 (1989); Martin et al., *Stress Ulcers and Organ Failure in Intubated Patients in Surgical Intensive Care Units,* ANN SURG., 215: 332-337 (1992)). In two recent meta-analyses (Cook et al., *Stress Ulcer Prophylaxis in the Critically Ill: A Meta-analysis,* AM. J. MED., 91: 519-527 (1991); Tryba, *Stress Ulcer Prophylaxis - Quo Vadis?* INTENS. CARE MED. 20: 311-313 (1994)) [Antacids] antacids, sucralfate, and H_2-antagonists were all found to be superior to placebo and similar to one another in preventing upper gastrointestinal bleeding. Yet, prophylactic agents are withdrawn in fifteen

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to twenty percent of patients in which they are employed because of failure to prevent bleeding or control pH (Ostro et al., *Control of Gastric pH With Cimetidine Boluses Versus Primed Infusions,* GASTROENTEROLOGY, 89: 532-537 (1985); Siepler, *A Dosage Alternative for H-2 Receptor Antagonists, Continuous-Infusion,* CLIN. THER., 8(SUPPL A): 24-33 (1986); Ballesteros et al., *Bolus or Intravenous Infusion of Ranitidine: Effects on Gastric pH and Acid Secretion: A Comparison of Relative Cost and Efficacy,* ANN. INTERN. MED., 112:334-339 (1990)), or because of adverse effects (Gafter et al., *Thrombocytopenia Associated With Hypersensitivity to Ranitidine: Possible Cross-reactivity With Cimetidine,* AM. J. GASTROENTEROL, [64] 84: 560-562 (1989); Sax, *Clinically Important Adverse Effects and Drug Interactions With H2-Receptor Antagonists: An Update,* PHARMACOTHERAPY 7(6 PT 2): 110S-115S (1987); Vial et al., *Side Effects of Ranitidine,* DRUG SAF, 6:94-117(1991); Cantu and Korek, *Central Nervous System Reactions to Histamine-2 Receptor Blockers,* ANN. INTERN MED., 114: 1027-1034 (1991); and Spychal and Wickham, *Thrombocytopenia Associated With Ranitidine,* BR. MED. J., 291: 1687 (1985)). In addition, the characteristics of an ideal agent for the prophylaxis of stress gastritis were analyzed by Smythe and Zarowitz, *Changing Perspectives of Stress Gastritis Prophylaxis,* ANN PHARMACOTHER, 28: 1073-1084 (1994) who concluded that none of the agents currently in use fulfill their criteria.--

3. The paragraph beginning on page 20, line 7, has been amended as follows:

-- Second, because bicarbonate is usually neutralized in the stomach or is absorbed, such that belching results, patients with gastroesophageal reflux may exacerbate or worsen their reflux disease as the belching can cause upward movement of stomach acid ([Brunton] Goodman AG, et al., *Agents for the Control of Gastric Acidity and Treatment of Peptic Ulcers,* [IN] in,

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[Goodman AG, et al. The Pharmacologic Basis of Therapeutics] THE PHARMACOLOGIC BASIS OF THERAPEUTICS (New York, p. 907 (1990)).--

4. The paragraph beginning on page 29, line 22, has been amended as follows:

-- The liquid oral pharmaceutical composition of the present invention is prepared by mixing omeprazole (Prilosec® AstraZeneca) or other proton pump inhibitor or derivatives thereof with a solution including at least one buffering agent (with or without a parietal cell activator, as discussed below). Preferably, omeprazole or other proton pump [inhibitor] inhibitors, which can be obtained from a capsule or tablet or obtained from the solution for parenteral administration, is mixed with a sodium bicarbonate solution to achieve a desired final omeprazole (or other PPI) concentration. As an example, the concentration of omeprazole in the solution can range from approximately 0.4 mg/ml to approximately 10.0 mg/ml. The preferred concentration for the omeprazole in the solution ranges from approximately 1.0 mg/ml to approximately 4.0 mg/ml, with 2.0 mg/ml being the standard concentration. For lansoprazole (Prevacid® TAP Pharmaceuticals, Inc.) the concentration can range from about 0.3 mg/ml to 10 mg/ml with the preferred concentration being about 3 mg/ml.--

5. The paragraph beginning on page 51, line 4, has been amended as follows:

-- Children are affected by gastroesophageal reflux disease (GERD) with atypical manifestations. Many of these atypical symptoms are difficult to control with traditional drugs such as H_2-antagonists, cisapride, or sucralfate. PPIs are more effective in controlling gastric pH and the symptoms of GERD than other agents. However, PPIs are not available in dosage forms that are easy to administer to young children. To address this problem, applicant employed

omeprazole or lansoprazole in a buffered chocolate suspension (Choco-Base™)[,] in children with manifestations of GERD.--

6. The paragraph beginning on page 51, line 15, has been amended as follows:

-- Applicant performed a retrospective evaluation of children with GERD referred to the University of Missouri-Columbia from 1995 to 1998 who received treatment with the experimental omeprazole or lansoprazole Choco-Base™ suspension formulated in accordance with Formulation 1 stated below. Data were included on all patients with follow up information sufficient to draw conclusions about pre/post treatment (usually > 6 months). There were 25 patients who met the criteria for this evaluation. Age range was several weeks to greater than 5 years. Most patients had a history of numerous unsuccessful attempts at ameliorating the effects of GERD. Medication histories indicated many trials of various drugs.--

7. The paragraph beginning on page 52, line 30, has been amended as follows:

--Of the 24 remaining patients, 18 were males and 6 were females. Ages at implementation of PPI therapy ranged from 2 weeks of age to 9 years old. Median age at start of therapy was 26.5 months [mean of 37 mo.] Early on, reflux was usually documented by endoscopy and confirmed by pH probe. Eventually, pH probe was dropped and endoscopy was the sole method for documenting reflux, usually at the time of another surgery (most often T-tubes or adenoidectomy). Seven patients had pH probe confirmation of GERD, whereas 18 had endoscopic confirmation of reflux including all eight who had pH probing done (See Graphs 1 and 2 below). Reflux was diagnosed on endoscopy most commonly by cobblestoning of the tracheal wall, with laryngeal and pharyngeal cobblestoning as findings in a few patients. Six

patients had neither pH nor endoscopic documentation of GERD, but were tried on PPI therapy based on symptomatology alone.--

8. The paragraph beginning on page 55, line 3, has been amended as follows:

-- Most patients responded favorably to and tolerated the once daily dosing of Choco-Base™ proton pump inhibitor suspension. Two patients had documented adverse effects associated with the use of the PPI suspension. In one patient, the mother reported increased burping up and dyspepsia, which was thought to be related to treatment failure. The other patient had small amounts of bloody stools per mother. This patient never had his stool tested, as his bloody stool promptly resolved upon cessation of therapy, with no further sequellae. The other 23 patients had no documented adverse effects.--

9. The paragraph beginning on page 64, line 3, has been amended as follows:

-- In all four of the above formulations, lansoprazole or other PPI can be substituted for omeprazole in equipotent amounts. For example, 300 mg of lansoprazole may be substituted for the 200 mg of omeprazole. Additionally, aspartame can be substituted for sucrose, and the following other ingredients can be employed as carriers, adjuvants and excipients: maltodextrin, vanilla, carragreenan, mono and diglycerides, and lactated monoglycerides. One skilled in the art will appreciate that not all of the ingredients are necessary to create a Choco-Base™ formulation that is safe and effective.--

10. The paragraph beginning on page 65, line 8, has been amended as follows:

--Applicant additionally analyzed the effects of a lansoprazole Choco-Base™ formulation on gastric pH using a pH meter (Fisher Scientific) in one adult patient versus lansoprazole alone.

The patient was first given a 30 mg oral capsule of Prevacid®, and the patient's gastric pH was measured at 0, 4, 8, 12, and 16 hours post dose. The results are illustrated in Fig. 4.--

11. The paragraph beginning on page 65, line 15, has been amended as follows:

-- The Choco-Base product was compounded according to Formulation 1 above, except 300 mg of lansoprazole was used instead of omeprazole. A dose of 30 mg lansoprazole Choco-Base™ was orally administered at hour 18 post lansoprazole alone. Gastric pH was measured using a pH meter at hours 18, 19, 24, 28, 32, 36, 40, 48, 52, and 56 post lansoprazole alone dose.--

12. The Table 4 on page 83 has been amended as follows:

--TABLE 4

'he average length of treatment was 9 days. Cost of care was calculated from these [date] days.

		Per Day	Total
)MEPRAZOLE (day 1)			
'roduct acquisition cost	40 mg load x 2 5.66/dose)	11.32	11.32
ıncillary product	materials for solution preparation	0.41	0.41
ıncillary product	syringe w/needle	0.20	0.40
¦terile preparation required	no		
¦OS preparation time (R.N.)	6 minutes	2.40	4.80
¦.N. time ($24/hr)	21 minutes/day (includes pH monitoring)	8.40	8.40
)MEPRAZOLE (days 2-9)			
'roduct [acqusition] acquisition cost	20 mg per day	2.80	22.65
ıncillary product	materials for solution preparation	0.41	0.82
ıncillary product	syringe w/needle	0.20	1.60
¦terile preparation required	no		
¦OS preparation time (R.N.)	6 minutes	2.40	4.80
¦.N. time ($24/hr)	18 minutes/day (includes pH monitoring)	8.40	57.60
/75 patient require 40 mg simplified [omeparzole] omeprazole solution per day (days 2-9)			0.63
Jo additional cost for adverse effects or for failure			
¦OTAL□	113.43		
¦implified [Omerprazole] Omeprazole Solution cost per day □	12.60		

Pharmacoeconomic evaluation of omeprazole cost of care--

13. The Table 5 on page 83 has been amended as follows:

TABLE 5

ime	Control	1 hour	24 hour	2 day	7 day	14 day
onc (mg/ml)	2.01	2.07	1.94	1.96	1.97	1.98

tability of Simplified Omeprazole Solution at room temperature
25° C.). Values are the mean of three samples.—

14. The paragraph beginning on page 84, line 21, has been amended as follows:

--(b) 20 mg of a liquid formulation of approximately 2 mg omeprazole per 1 ml of 8.4% sodium bicarbonate[.];--

15. The paragraph beginning on page 86, line 16, has been amended as follows:

-- Blood samples will be centrifuged within 2 hours of collection and the plasma will then be separated and frozen at –10° C (or lower) until assayed. Pharmacokinetic variables will include: time to peak concentration, mean peak concentration, AUC (0-t) and (0-infinity). Analysis of variance will be used to detect statistical difference. Bioavailability will be assessed by the 90% confidence interval of the two one-sided tests on the natural logarithm of AUC.--

16. The paragraph beginning on page 86, line 26, has been amended as follows:

-- Omeprazole and internal standard (H168/24) will be used. Omeprazole and internal standard will be measured by modification of the procedure described by Amantea and Narang. (Amantea MA, Narang PK. Improved Procedure for Quantification of Omeprazole and Metabolites Using Reversed-Phased High Performance Liquid Chromotography. J. CHROMATOGRAPHY 426; 216-222. 1988). Briefly, 20[ul] □l of omeprazole 2mg/ml NaHCO3 or Choco-Base™ omeprazole suspension and 100[ul] □l of the internal standard are

vortexed with 150[ul] ☒ of carbonate buffer (pH=9.8), 5 ml of dichloromethane, 5 ml of hexane, and 980 [ul] ☒ of sterile water. After the sample is centrifuged, the organic layer is extracted and dried over a nitrogen stream. Each pellet is reconstituted with 150 [ul] ☒ of mobile phase (40% methanol, 52% 0.025 phosphate buffer, 8% acetonitrile, pH=7.4). Of the reconstituted sample, 75[ul] ☒ is injected onto a C18 5 U column equilibrated with the same mobile phase at 1.1ml/min. Under these conditions, omeprazole is eluted at approximately 5 minutes, and the internal standard at approximately 7.5 minutes. The standard curve is linear over the concentration range 0-3 mg/ml (in previous work with SOS), and the between-day coefficient of variation has been <8% at all concentrations. The typical mean R2 for the standard curve has been 0.98 in prior work with SOS (omeprazole 2mg/ml NaHCO3 8.4%).--

17. The paragraph beginning on page 89, line 6, has been amended as follows:

-- A solution was prepared by mixing 8.4% sodium bicarbonate with omeprazole to produce a final concentration of 2 mg/ml to determine the stability of omeprazole solution after 12 months. The resultant preparation was stored in clear glass at room temperature, refrigerated and frozen. Samples were drawn after thorough agitation from the stored preparations at the prescribed times. The samples were then stored at 70°C. Frozen samples remained frozen until they were analyzed. When the collection process was completed, the samples were shipped to a laboratory overnight on dry ice for analysis. Samples were agitated for 30 seconds and sample aliquots were analyzed by HPLC in triplicate according to well known methods. Omeprazole and the internal standard were measured by a modification of the procedure described by Amantea and Narang. Amantea MA, Narang PK, Improved Procedure For Quantitation Of Omeprazole And Metabolites Using Reverse-Phased High-Performance Liquid Chromatography, J. Chromatography, 426: 216-222 (1988). Twenty (20) [ul] ☒ of the omeprazole 2mg/ml

NaHCO3 solution and 100 [ul] ☑ of the internal standard solution were vortexed with 150 [ul] ☑ of carbonate buffer (pH = 9.8), 5 ml dichloromethane, 5 ml hexane, and 980 [ul] ☑ of sterile water. The sample was centrifuged and the organic layer was extracted and dried over a nitrogen stream. Each pellet was reconstituted with 150 [ul] ☑ of mobile phase (40% methanol, 52% 0.025 phosphate buffer, 8% acetonitrile, pH=7.4). Of the reconstituted sample, 75[ul] ☑ were injected onto a C185u column equilibrated with the same mobile phase at 1.1 ml/min. Omeprazole was eluted at ~5 min, and the internal standard at ~7.5 min. The standard curve was linear over the concentrated range 0-3 mg/ml, and between-day coefficient of variation was < 8% at all concentrations. Mean R2 for the standard curve was 0.980.--